COMPARING SURVIVAL BETWEEN BLACK AND WHITE CASTRATION-RESISTANT PROSTATE CANCER PATIENTS TREATED WITH DOCETAXEL IN PHASE III CLINICAL TRIALS

by

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Abstract

Background

Black men have higher prostate cancer incidence and mortality compared to white men. Both biological and socioeconomical factors contribute to the disparity in prostate cancer mortality. Fewer studies focus on the racial disparity in advanced prostate cancer compared to that of early disease. Data from clinical trials provide an opportunity to study racial disparity in cancer outcome in a controlled setting. Generating evidence on the racial disparity in advanced prostate cancer outcome from clinical trial data could help understand the disease and lead to more precise treatment guidelines.

Materials and Methods

Individual patient data of black and white men who received docetaxel from the comparator arm of four phase III CRPC trials [ASCENT2 (NCT00273338), VENICE (NCT00519285), ENTHUSE-M1C (NCT00617669), and MAINSAIL (NCT00988208)]. Comparison of overall survival (OS) between black vs white men was performed by the Kaplan-Meier method, log-rank test, and mixed-effect Cox models. The prognostic value of PSA response was assessed by mixed-effect Cox models. Incidence of PSA response was assessed by mixed-effect logistic regression models. Missing lab data was imputed using the Markov chain Monte Carlo method.

Results

A total of 1817 patients were included in the analysis; 1721 (94.7%) were white and 96 (5.3%) were black. No difference in OS by race was detected by log-rank test (P=0.708). The hazard ratio of death comparing black to white men was 0.86 (95% CI 0.62-1.19, P=0.339) after adjusted by age, trial of enrolment, site of metastases, prior treatment and baseline lab data. The hazard ratio of death comparing patients with and without PSA response was 0.78 (95% CI 0.42-1.45, P=0.423) in black

men and 0.54 (95% CI 0.47-0.62, P<0.001) in white men. The incidence of PSA response was higher in black men compared to that in white men (odds ratio 1.30, 95% CI 1.17-1.46, P<0.001).

Conclusions

In the 4 CRPC trials, OS in black men was insignificantly longer to that of white men. PSA response was a strong favorable prognostic indicator in white men, but not found in blacks. Black men had a significantly higher incidence for having PSA response.

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1 Introduction

In the United States, prostate cancer is the most common cancer and the third leading cause of cancer death in men, accounting for more than 170,000 new cases and 30,000 deaths annually [1]. Racial disparities in prostate cancer incidence and mortality, especially between black and white men are well recognized. Black men have a higher prostate cancer incidence (157.6 vs 93.9 per 100,000 in 2015) and mortality (37.5 vs 17.7 per 100,000 in 2015) compared to white men in the US [2 1]. Between 2010 and 2012, the lifetime risk of developing and dying from prostate cancer was 18.2% and 4.4% in black men, whereas the risks were 13.3% and 2.4% in white men [2]. The age of prostate cancer diagnosis was found to be earlier in black men compared to white men [3,4], and prostate cancer transforms to aggressive disease earlier in black men [5]. In addition to earlier development of aggressive disease, higher pathologic upgrading rate and biochemical recurrence after definitive treatment in lower risk groups could be potential explanations of the higher mortality rate in black men [6-8]. Prior studies found that the expression of genes associated with prostate cancer and tumor immunology, as well as the location of the tumors, were different between black and white men, indicating that biological difference could contribute to the racial disparity in prostate cancer outcome [9-11]. Socioeconomic factors could also play a role, as the differences between black and white men in the intensity of prostate-specific antigen (PSA) screening/surveillance, access to and choice of treatment, and diet between black and white men partially explains the gap in prostate mortality [12.13].

Prior studies on the racial disparity in prostate cancer outcome heavily focused on localized disease, whereas evidence on advanced prostate cancer remains limited. Polednak compared the survival of 24,136 white men and 3,817 black men with late-stage (defined as disease that

spread beyond the prostatic capsule) prostate cancer using data from the Surveillance, Epidemiology, and End Result (SEER) program [14]. The hazard ratio (HR) for prostate cancer death comparing black to white patients was 1.44 (95% Ci 1.35-1.53). After adjusting for age, disease extent, marital status and surgery, the effect of race became non-significant (HR 1.05 95% CI 0.99-1.12). Despite that the study had a substantial sample size, it did not adjust for known clinical prognostic factors, such as Gleason score, PSA level, response to androgen-deprivation therapy, and other socioeconomic information. The quality of the data also depended on the accuracy of the SEER codes. These are common issues using registry data. To further isolate the biological and socioeconomic effects that contribute to the racial disparity in advanced prostate cancer outcome, a well-controlled setting is required.

Data from clinical trials provide an opportunity to study racial disparity in prostate cancer outcome in a controlled setting. Patients enrolled in clinical trials are more homogenous in disease status and baseline characteristics, allowing the effect of race to be isolated more easily. The information collected in clinical trials is often more reliable and complete, which allows detailed adjustment for covariables and lead to higher validity [15]. The major challenge of using clinical trial data to address racial disparity in prostate cancer is the racial composition of prostate cancer trial participants. Less than 10% of the study participants were nonwhite in the market approval of prostate cancer trials between 1993 and 2013 [16]. While comprising approximately 15% of newly diagnosed prostate cancer cases in the US, only around 5% of prostate cancer clinical trial participants were black men [16,17]. Possible reasons for the underrepresentation of black men in cancer trials include lack of trust between the minority patients and the medical community, negative beliefs about participation in clinical trials, lack of knowledge regarding clinical trials, influence of healthcare providers on trial participation, and recommendation from friends or relatives with prior experience of

participation [16,18,19]. To have a reasonable sample size for examining the racial disparity in prostate cancer outcome often requires pooling of multiple clinical trial data.

A small number of studies compared the outcome between black and white men with advanced prostate cancer using clinical trial data. Thompson et al. analyzed data from 288 African-American and white men in the Southwest Oncology Group Study (SWOG) 8894, in which orchiectomy with or without flutamide was compared in men with metastatic prostate cancer. After adjusting for performance status, age, Gleason score, and PSA level, African-American men had a significantly unfavorable OS compared to white men (HR 1.23, 95% CI 1.04-1.47, p=0.018) [20]. Catherine et al. have drawn a similar conclusion in a study using patient data from SWOG 8894 and SWOG 9346 [21]. Among the 2,587 men with metastatic, hormone-naive prostate cancer included in the analysis, 504 (19%) were African-American men. The HR for death comparing African-American to non-African-American men was 1.30 (95% CI 1.10-1.54, p=0.003) after adjusting for disease extent, pain, PSA level, age, performance status, Gleason score, and weight. However, results from three studies suggested a possible opposite effect of race in patients with metastatic castration-resistant prostate cancer (mCPRC). Halabi et al. pooled data from four phase III and four phase II CRPC trials conducted by the Cancer and Leukemia Group B (CALGB) to analyze racial disparity on survival. After adjusting for known prognostic variables, no statistically difference in Overall survival (OS) was found between black and white men, although black men had a slightly lower risk for death (HR for death 0.85, 95% CI 0.71-1.02, p=0.08) [22]. Another study conducted by the same group that included eight CALGB CRPC trials found that black race was a favorable prognostic factor (HR 0.77, 95% CI 0.65-0.91, p=0.004) [23]. In the two pooled analyses mentioned above, patient received various treatment; therefore, the effect of the treatment could confound the results. While we are doing working on the present study, a

study that addressed the effect of race on survival following docetaxel treatment was published [24]. Among 500 black and 7,528 white patients with CRPC who were assigned to docetaxel and prednisolone treatment from nine phase III clinical trials, black men had a lower risk of death compared to white men (HR 0.81, 95% CI 0.72-0.91, p<0.001) after adjusting for age, PSA, performance status, alkaline phosphatase (ALP), hemoglobin (Hb) and site of metastases. The effect was even more prominent in four National Clinical Trial Network trials, which included 287 black men and 2,022 white men (HR 0.71, 95% CI 0.58-0.87, p<0.001). These findings raise the question of whether racial disparity in prostate cancer outcome differs across the disease course. We would also like to understand the interactions between effect of race and important prognostic factors (i.e. age and visceral metastasis) on survival, which were not explored in prior studies. Further investigation is warranted to understand the mechanism behind the racial disparity in CRPC outcome.

The dynamics of PSA after treatment is widely recognized as a prognosis indicator in advanced prostate cancer, but whether it could serve as a surrogacy remains controversial. An analysis based on the data from the SWOG 9916 trial found that a ≥30% decrease of PSA was associated with a 50% decrease of risk of death [25]. Armstrong et al. found that PSA decline was highly prognostic in the TAX327 trial, but it was a weak surrogate for survival after taking the effect of treatment into account [26]. Another study, which collected 2,161 individual patients' data from studies comparing bicalutamide to castration in patients with metastatic prostate cancer, concluded that time to PSA progression, PSA decline ≥50% and PSA normalization were prognostic indicators, but not ideal surrogates for OS [27]. In a study by Francini et al., which included data from 22 clinical trials using docetaxel-based first-line therapy for CRPC, found a statistically significant but low correlation between PSA response rate and OSl (correlation coefficient ρ=0.50, 95% CI 0.47-0.88, p=0.003) [28]. Replacing OS

with PSA dynamic parameters as the primary endpoint of prostate cancer clinical trials is not generally accepted [29]. Despite the controversy on the surrogacy value of these PSA indicators, assessing differences between blacks and whites in the dynamics of PSA response could potentially help us understand the racial disparity in advanced prostate cancer outcome.

In the present study, we aimed to compare the OS of black and white men with CRPC using clinical trial data to evaluate if there is racial disparity in the effect of docetaxel treatment on CRPC outcome. In order to understand whether the effect of race differs across patient groups, we explored the interaction between race and important prognostic variables (age and extent of the disease) on OS. Another aim of our study was to explore the possible mechanisms of racial disparity in CRPC outcome by examining PSA response, which is defined as a 50% decrease of PSA from baseline from two consecutive tests ≥3 weeks apart within 12 weeks of treatment initiation [30].

2 Materials and Methods

2.1 Source of the dataset

All the data in this study were obtained from Project Data Sphere. Project Data Sphere is an independent, nonprofit organization, which serves as a platform for researchers to share and analyze historical, individual-level phase III oncology trial comparator arm data. The site does not provide data from the experimental arms of the trials. The platform is accessible to academic institutions, hospitals, and life science company affiliates, as well as independent researchers. The organization is operated and funded by the CEO Roundtable on Cancer's Life Sciences Consortium[31].

2.2 Study Population

Clinical trials available on Project Data Sphere, which enrolled metastatic CRPC patients treated with docetaxel, and who had not received prior chemotherapy were selected for analysis. To further minimize the heterogeneity of the study population trials having additional therapeutic agents other than a placebo in the comparator arm were excluded.

2.3 Data harmonization

Project Data Sphere provides researchers de-identified, individual-level trial data. The content and format of the datasets vary among clinical trials. A master dataset was created to hold all information collected from the eligible trials. Items in the master dataset included age, race/ethnicity, overall survival, outcome (death), initial staging, Gleason Score, baseline laboratory data, prior therapy, disease extent (bone, lymph node, and visceral organ involvement), PSA response during therapy. Race/ethnicity of the patients was categorized into white, black, Hispanic, Asian and others. As not all trials provided the exact age of the patient, age was categorized into three groups: 18 to 64 years, 65 to 74 years, and 75 years and above. Overall survival was defined as the time from the date of randomization to the date of death. Baseline laboratory data was defined as laboratory tests taken within 14 days prior to randomization; if multiple lab tests were taken within the defined period, the lab test closest to randomization would be recorded as baseline. A PSA response was defined as having a greater or equal to 50% PSA decline from the baseline PSA level within 12 weeks of the date of randomization.

2.4 Imputation of missing values

In order to retain the power of the analyses, Markov chain Monte Carlo (MCMC) method was used to impute missing laboratory data [32], approximating the distribution of the observed variables. Before MCMC imputation, all laboratory data were natural log transformed to avoid generation of negative values from the imputation. Baseline laboratory data and important clinical characteristics were included in the imputation model.

2.5 Comparison of baseline characteristics

Comparison of baseline characteristics was performed between black and white patients. Chi-square test was used to compare ordinal variables. Wilcoxon rank-sum test was used to compare continuous variables. Comparison of imputed and unimputed laboratory data was also performed using Wilcoxon rank-sum test.

2.6 Comparison of overall survival

The overall survival of the patient groups was estimated by the Kaplan-Meier method and statistical significance was assessed by log-rank test. A random-effect model was used to estimate the hazard ratio pooled over the trials. The effect of variables on overall survival was performed using mixed-effect Cox proportional hazard model. The fixed effects of the primary variable of interest: race (black vs white), as well as age, disease stage, and extent, prior therapy, baseline laboratory data were analyzed in the models, whereas the random effect of the individual clinical trials was also tested. The interaction between race and other variables was tested by adding an interaction term to the selected Cox models.

2.7 Selection of the Cox models

A Cox model using the imputed dataset that included all variables was first constructed. A stepwise approach by taking out one variable at a time, starting from the least significant one, was performed to select the desirable model. Non-significant variables that alter the HR for the main effect of interest (black vs white) by equal or greater than 3% were included in the model. Significant variables that change the main effect of interest by less than 3% were dropped from the model. Age and visceral disease were fixed in the model regardless of significance. The next step was to construct the final model, which included the previously selected variables but excluded those having a missing value greater than 10%, using non-imputed data. A sensitivity analysis comparing the main effect of interest between the final model and the one using imputed data was performed.

2.8 Prognostic value of PSA response on overall survival

The prognostic value of PSA response was tested using the mixed-effect Cox model. PSA response was added as a fixed-effect variable in the selected Cox model described in the prior section. The difference in prognostic value of PSA response between race was examined by an interaction model. The fit of the original (main effects) model vs. the interaction model was compared using likelihood ratio test.

2.9 The incidence of PSA response

A mixed-effect logistic regression model was used to test the difference in incidence of PSA response between black and white race. The same stepwise approach described in the "Selection of Cox models" section was used for selecting the desirable logistic regression model. The interaction between race and other variables was tested by adding an interaction term to the selected logistic regression models.

3 Results

3.1 Trials selected for analyses

Data from 13 CRPC trials were accessible from Project Data Sphere. Twelve of the thirteen trials enrolled patients with metastatic CRPC, and among those, nine focused on patients who had not received prior chemotherapy. Docetaxel and prednisone (with or without an additional placebo) were given as the comparator arm treatment in four trials [ASCENT2 (NCT00273338), MAINSAIL (NCT00988208), VENICE (NCT00519285), and ENTHUSE-M1C (NCT00617669)]. Individual-level, de-identified patient data from the four trials were included for analyses (Table 1).

3.2 Patient demographics

A total of 2070 men were in the comparator arm of the four trials, including 1721 white, 96 black, 14 Hispanic, 115 Asian, and 69 men of other race. The race of fifty-five out of the 2070 men was missing. The age distribution, BMI, proportion of visceral and bone disease, prior therapy received were similar between white and black patients. Black men had a significantly lower proportion of lymph node or soft tissue disease; lower baseline hemoglobin and total bilirubin concentration; higher baseline PSA level, serum calcium concentration, serum creatinine, blood lymphocyte count, and serum creatinine (Table 2).

3.3 Imputation of laboratory data

All laboratory data were natural log transformed before MCMC imputation. Variables included in the MCMC model were the individual trial, age, race, presence of visceral disease, baseline PSA, ALP, LDH, albumin, total-bilirubin, analine aminotransferase

creatinine, hemoglobin, platelet count, and neutrophil/lymphocyte ratio. The number of imputed values generated for each lab variable is in Table 3.

3.4 Comparison of overall survival between black and white men

The median OS for black and white patients was 651 days (95% CI 588-743) and 592 days (95% CI 568-651), respectively (Fig. 1). No difference in OS was detected between the two races by log-rank test (P=0.708). The hazard ratio for death, comparing black to white race was 0.63 (95% CI 0.3-1.35) in the ASCENT-2 trial, 0.67 (0.24-1.85) in the MAINSAIL trial, 0.94 (95% CI 0.55-1.61) in the VENICE trial, and 1.21 (0.77-1.91) in the ENTHUSE-M1C trial. The combined hazard ratio in the random effect model was 0.96 (95% CI 0.71-1.31, p=0.454) (Fig. 2). The hazard ratio for death, comparing black to white race in the unadjusted, mixed-effect Cox model was 0.90 (95% CI 0.67-1.22, p=0.510). After stepwise selection, the variables included in the model using imputed data were race, age, baseline PSA, ALP, LDH, Hb, receipt of prior gonadotropin, visceral disease and lymph node and/or soft tissue disease. As LDH was the only variable with a missing value greater than 10%, it was taken out from the model using the non-imputed data. Comparing the effect of race on OS between the model using the imputed data and the model without LDH using the non-imputed data, the difference in hazard ratio was less than 3% (HR 0.88 vs 0.86). Thus, the model using the non-imputed data was the final Cox model (Table 4). Overall, OS was comparable between black and white men across models. Black men had a slightly lower hazard of death, but the effect was non-significant.

3.5 Interaction between race and age; race and visceral disease on overall survival

The interaction models were based on the final Cox model. The hazard ratios for death, comparing black and white men in the 18-64 years, 65-74 years, and ≥ 75 years age groups

were 0.82 (95% CI 0.48-1.41, p=0.477), 1.10 (95% CI 0.71-1.72, p=0.670), and 0.51 (0.23-1.15, p=0.104). A trend of favorable survival in black men older or equal to 75 years was identified, but the interaction was not significant (Table 5.). No significant interaction between race and visceral disease was detected. The hazard ratios for death comparing black to white men in visceral disease and non-visceral disease were 0.96 (95% CI 0.42-2.17, p=0.917) and 0.84 (95% CI 0.60-1.19, p=0.323) (Table 6). The fit of the model was not significantly improved in the interaction models after examined by likelihood ratio test (p=0.219 for the race*age model; p=0.777 for the race*visceral disease model).

3.6 Prognostic value of PSA response

PSA response was added as an independent variable to the final Cox model. The hazard ratio for death comparing patients with PSA response to those without was 0.55 (95% CI 0.48-0.63, p<0.001) in all patients, 0.54 (95% CI 0.47-0.62, p<0.001) in white men, and 1.00 (95% CI 0.49-2.05, p=0.997) in black men. To test whether there is a difference in the prognostic value of PSA response between black and white men, an interaction term between race and PSA response was added to the model. The overall survival difference between PSA responders and non-responders was more prominent in white men compared to black men (Table 7 and Fig. 3). However, the interaction term (p=0.258) and the likelihood ratio test (p=0.259) comparing the interaction model to the original model were not significant.

3.7 Incidence of PSA response

The odds ratio for PSA response, comparing black to white men was 1.21 (95% CI 0.47-2.66) in the ASCENT-2 trial, 0.98 (0.42-2.27) in the MAINSAIL trial, 1.46 (95% CI 0.52-4.08) in the VENICE trial, and 1.12 (0.47-2.66) in the ENTHUSE-M1C trial. The combined odds ratio in the random effect model was 1.16 (95% CI 0.74-1.81, p=0.454) (Fig. 4). The odds for

having PSA response was higher in black men compared to white men in the unadjusted mixed-effect logistic regression model (Odds ratio: 1.14, 95% CI 1.00-1.29, p=0.044). After stepwise selection, the variables included in the mixed-effect logistic regression model using imputed data were race, age, baseline PSA, ALP, LDH, Hb, total bilirubin, creatinine, visceral disease and receipt of radiation therapy. As LDH was the only variable with a missing value greater than 10%, it was taken out from the model using the non-imputed data. Comparing the effect of race on the incidence of PSA response between the model using the imputed data and the model without LDH using the non-imputed data, the difference in odds ratio was less than 3% (OR 1.29 vs 1.30). Thus, the model using the non-imputed data was selected as the final logistic regression model (Table 8). Overall, black men were more likely to have a PSA response during docetaxel/prednisone treatment compared to white men across models.

3.8 Interaction between race and age; race and visceral disease on PSA response

The interaction models were based on the final logistic regression model. Black men were more likely to have PSA response compared to white men within the three age groups, particularly forages 18-64 years (OR 1.70, 95% CI 0.98-2.96, p=0.060), but the effects were not significant (Table 9). The interaction terms between race and age were non-significant (race*65-74yr: p=0.211; race*≥75yr: p=0.514) and did not improve the fit of the model (likelihood ratio test p=0.632). Black men had a higher tendency to have PSA response compared to white men in both visceral disease (OR 1.27, 95% CI 1.13-1.43, p<0.001) and non-visceral disease (OR 1.61, 95% CI 0.88-2.96, p=0.124) (Table 10). The interaction term between race and visceral disease was not significant (p=0.486) and adding it did not significantly increase the fit of the model (likelihood ratio test p=0.732)

3.9 Summary of results

Overall, among patients enrolled in the comparator arm of the four CRPC trials, black men had a non-significantly more favorable OS compared to white men. The effect was consistent across age groups and patients with or without visceral disease (Fig.5). Having PSA response within 12 weeks of randomization was a strong favorable prognostic indicator in white men, but not in black men (Fig. 6). Black men had a significantly higher tendency for having PSA response. A similar effect was observed in all age groups and patients with or without visceral disease (Fig. 7).

4 Discussion

In the present study, we examined the effect of race, comparing black to white men, on the overall survival of docetaxel treated patients with CRPC using data from the comparator arm of four phase III clinical trials. Given that all patients analyzed were chemotherapy-naive before trial enrollment and were assigned to docetaxel and prednisone, we were able to isolate the effect of race in a setting with fewer confounders. The detailed history of prior therapy, the extent of the disease and baseline lab data recorded in clinical trials allowed adjustment for prognostic factors and increased validity.

Data from the four CRPC trials included in the present study suggested that black men had a significantly higher baseline PSA level and lower baseline Hemoglobin. These findings were consistent with those from prior studies [22,24,33,34]. However, no difference in ALP, LDH, and proportion of visceral metastasis was found between the two races in the present or the two prior studies. The discordance between the PSA, Hemoglobin and the other disease severity

indicator might suggest that the racial difference of baseline PSA and hemoglobin is biological. This hypothesis is supported by prior studies that addressed racial differences in serum PSA and hemoglobin [35,36].

We found a comparable OS between black and white CRPC patients (651 vs 592 days, p=0.708), and a tendency of lower risk of death in black men, though not statistically significant (HR 0.86, 0.62-1.18). The findings aligned with prior evidence [22-24]. The recent study by Halabi et al. included three of the four trials in the present study along with six other trials; patients in both experimental and control arms were included for analysis to reach a sizable black patient number. The favorable outcome in black men was significant in their analyses, but the effect size (HR 0.81 0.72-0.91, p<0.001) was similar to our result. When the trials were examined separately, the risk of death in black men was significant in only two out of the nine trials, suggesting that the effect is relatively small and could be heterogeneous across trials[24]. We also analyzed whether the effect of race differs across age and in the presence of visceral metastasis via interaction models, which was not performed in previous similar studies. The difference in risk of death seemed to be most prominent in patients ≥75 years, but the sample size within the subgroup was small to make such interpretation. As Halabi et al. demonstrated that the risk of death differs between age groups, it would be worth exploring the interaction of race and age within a larger population. On the other hand, the effect of race on OS was similar in patients with or without visceral metastases.

Following the prior studies that suggested a better outcome in black men with CRPC, the current attempted to explore the mechanism of such findings by comparing PSA response between black and white patients. We found that black men were more likely to have a PSA response than white men (OR 1.30, 95% CI 1.17-1.46, p<0.001). This was observed

consistently across age groups and patients with or without visceral metastases. The majority of studies on the racial disparity in serum PSA level focused on men without prostate cancer and its application on PSA screening [35,37,38]. There are limited data on the racial disparity in PSA dynamics after treatment in prostate cancer. A study found that PSA nadir and PSA doubling time after hormone therapy or hormone therapy withdraw did not differ between black and white men [39]. Another study showed that PSA outcome after radical prostatectomy was comparable between black and white patients [40]. In a small case series, PSA decline in black men with locally advanced prostate cancer was similar to that of white men after neoadjuvant chemohormonal therapy [41]. McGuire et al. showed that African-American men were less likely to experience normalization of PSA after neoadjuvant androgen deprivation therapy [42]. Possibly the only published data to date on the racial disparity in PSA dynamics after CRPC treatment is a case-control study by Ramalingam et al. [43]. White patients with CRPC diagnosed at a medical center between 2008 and 2015 were matched 2:1 to black patients as control based on docetaxel exposure. The proportion of PSA response was significantly higher in black men compared to white men (68.9% vs 48.9% p=0.028). Despite studying treatments other than docetaxel, the higher proportion of PSA response in black men in these studies aligned with our findings. As PSA response was identified as a prognostic factor for prostate cancer [25-28], the higher tendency of having PSA response in black men could be one explanation to their favorable survival.

Interestingly, we found that the prognostic value of PSA response may be different between black and white men in the interaction model. While PSA response was a strong favorable indicator for survival in white men (HR for death 0.54, 95% CI 0.47-0.62, p<0.001), the effect was non-significant in black men (HR 0.78 95% CI 0.42-1.45, p=0.423). To our

knowledge, the present study is the first to address this issue. The mechanism and implication of this observation warrant further investigation.

The major limitation of the present study was the small number of black CRPC patients included, which hindered the power of the analyses. The data used in the study was limited to that available from the Project Data Sphere and the sample size further lowered after we restricted to patients who received docetaxel and prednisone. We believe that a valid inference could only be made in a controlled clinical trial setting, in which the influence of residual confounders is minimized by randomization. The different definition of race could be a limitation. The four trials included in the study enrolled participants over a wide geographic region, including America, Europe, and Asia, and the definition of black race may vary across trials. Only one of the four trials differentiated non-Hispanic white with Hispanic white, thus the composition of white men in this study could also be heterogeneous. Another challenge with the dataset was missing data. Potential prognostic variables such as prior surgical history (prostatectomy, orchidectomy), body-mass index, LDH, albumin neutrophil-lymphocyte ratio were not collected in one or more of the trials. In order to retain sample size while including important variables with a high proportion of missing values, we used multiple chain imputation for missing lab data. But, a sensitivity analysis showed that the main effect of interest was not altered when using imputed data.

Only 5% of the study population was black; the proportion was similar to that previously reported [16]. Underrepresentation of black patients in cancer clinical trials could be attributed to various socioeconomic and cultural factors [18,19]. The aim of the present study was not only to add knowledge to the racial disparity in CRPC but also to raise awareness of the underrepresentation of black men in prostate cancer trials. There has been growing evidence,

including that provided in this study, indicating that black men participated in CRPC trials have comparable or even more favorable outcome [22-24]. We hope that delivering such information to both the black community and physicians will foster participation as well as enrollment of black men into prostate cancer trials.

5 Figure Legend

Table 1. Information on the four CRPC trials included for analysis

	ASCENT-2	**MAINSAIL**	**VENICE**	**ENTHUSE-M1C**
ClinicalTrials.gov registry number	NCT00273338	NCT00988208	NCT00519285	NCT00617669
Clinical setting	CRPC, chemotherapy-naive	CRPC, chemotherapy-naive	CRPC, chemotherapy-naive	CRPC, chemotherapy-naive
Comparator arm treatment	Docetaxel Prednisone	Placebo Docetaxel Prednisone	Placebo Docetaxel Prednisone	Placebo Docetaxel Prednisone
No. of pts. in the comparator arm by race, N (%)				
White	419 (88)	433 (92)	538 (97)	331 (70)
Black	32 (7)	25 (5)	17 (3)	22 (6)
Hispanic	14 (3)	0 (0)	0 (0)	0 (0)
Asian	5 (1)	0 (0)	36 (6)	74 (16)
Other	7 (1)	13 (3)	7 (1)	43 (9)
Participating countries/regions	Canada, Czech Republic, Former Serbia and Montenegro, Germany, Hungary, Puerto Rico, Romania, Slovakia, United States	Argentina, Australia, Brazil, Canada, Czech Republic, Finland, France, Germany, Hungary, India, Italy, Korea, Netherlands, Peru, Poland, Portugal, Romania, Russian Federation, Serbia, South Africa, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States	Argentina, Australia, Belgium, Brazil, Canada, Chile, Croatia, Czech Republic, Denmark, Estonia, France, Germany, Hong Kong, Hungary, Israel, Italy, Korea, Netherlands, Poland, Portugal, Russian Federation, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Turkey, Ukraine, United Kingdom, United States	Argentina, Australia, Brazil, Canada, Czech Republic, Finland, France, Germany, Hungary, India, Italy, Korea, Netherlands, Peru, Poland, Portugal, Romania, Russian Federation, Serbia, South Africa, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States

Table 2. Baseline characteristics of patients, grouped by race

	Black N=96	White N=1721	P-value	Missing %
Age group, N (%)				
18-64 years	34 (31)	532 (35)		
65-74 years	42 (45)	783 (44)	0.622	--
≥75 years	20 (24)	406 (21)		
BMI (m^2/kg), median (IQR)	27.9 (24.6-31.0)	27.8 (25.3-30.8)	0.956	362 (20)
Disease extent, N(%)				
Visceral metastasis	12 (13)	319 (19)	0.136	--
Bone metastasis	79 (81)	1468 (85)	0.278	--
Lymph node/soft tissue metastasis	34 (35)	827 (48)	0.016	--
Prior therapy				
Gonadotropin (ADT)	71 (76)	1353 (79)	0.425	10 (1)
Anti-androgen	63 (67)	1289 (75)	0.074	10 (1)
Glucocorticoid	33 (35)	631 (37)	0.735	10 (1)
Corticosteroid	8 (9)	181 (11)	0.526	10 (1)
Bisphosphonate	31 (33)	651 (38)	0.328	10 (1)
Imidazole	12 (13)	160 (9)	0.271	10 (1)
Estrogen	5 (5)	148 (9)	0.260	10 (1)
Radiation therapy	54 (56)	1026 (60)	0.513	--
Prostatectomy	18 (24)	406 (29)	0.367	353 (19)
Orchidectomy	15 (20)	222 (16)	0.328	353 (19)
Baseline lab data, median (IQR)				
PSA (ng/mL)	123 (49-416)	85 (31-243)	0.010	18 (1)
ALP (U/L)	121 (85-218)	126 (83-260)	0.634	19 (1)
Ca (mmol/L)	2.38 (2.33-2.47)	2.34 (2.25-2.42)	<0.001	24 (1)
LDH (U/L)	200 (180-236)	208 (176-269)	0.711	598 (33)
Albumin (g/L)	42 (39-44)	43 (40-45)	0.308	481 (27)
Neutrophil (K/mm^3)	4.40 (3.01-6.01)	4.70 (3.60-6.52)	0.060	46 (3)
Lymphocyte (K/mm^3)	1.56 (0.79-2.06)	1.09 (0.73-1.61)	0.020	1040 (57)
Hemoglobin (g/dL)	11.9 (11.0-12.9)	12.7 (11.6-13.6)	<0.001	34 (2)
Creatinine (μmol/L)	97 (80-111)	82 (71-97)	<0.001	17 (1)
Total-bilirubin (μmol/L)	5.13 (3.21-8.55)	7.00 (5.00-9.00)	0.001	36 (2)

Table 3. Missing laboratory values

Variables	Observations		
	Complete	Incomplete	Imputed
PSA	1798	19	19
ALP	1798	19	19
LDH	1219	598	598
ALT	1789	28	28
Albumin	1336	481	481
Hemoglobin	1783	34	34
N/L ratio	773	1044	1044
Platelet	1771	46	46
Creatinine	1800	17	17
Total-bilirubin	1781	36	36

Table 4. Mixed-effect Cox models on OS

	Full model, imputed data†			Selected model, imputed data†			Selected model, non-imputed data*†		
No. of patients	1807			1807			1751		
No. black/white	94/1713			94/1713			89/1662		
Variables	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Race (black vs white)	0.87	0.63-1.20	0.388	0.88	0.64-1.20	0.416	0.86	0.62-1.18	0.339
Age group									
18-64	1	--	--	1	--	--	1	--	--
65-74	0.90	0.77-1.05	0.186	0.92	0.79-1.07		0.91	0.78-1.06	0.209
≥ 75	1.03	0.85-1.25	0.759	1.06	0.88-1.28		1.05	0.87-1.26	0.624
PSA	1.05	1.00-1.11	0.035	1.05	1.00-1.10	0.047	1.05	1.00-1.10	0.045
ALP	1.36	1.22-1.51	<0.001	1.35	1.22-1.50	<0.001	1.42	1.30-1.54	<0.001
LDH	1.21	0.93-1.57	0.148	1.21	0.94-1.56	0.138			
Albumin	0.43	0.20-0.91	0.028						
Hb	0.23	0.11-0.46	<0.001	0.18	0.10-0.34	<0.001	0.16	0.09-0.28	<0.001
N/L ratio	1.04	0.92-1.18	0.471						
Creatinine	1.08	0.81-1.44	0.583						
Total-bilirubin	1.00	0.85-1.17	0.962						
Anti-androgen	1.06	0.86-1.32	0.572						
Glucocorticoid	0.88	0.68-1.13	0.315						
Gonadotropin	0.73	0.62-0.87	<0.001	0.75	0.64-0.89	0.001	0.77	0.65-0.92	0.003
Bisphosphonate	0.91	0.79-1.05	0.197						
Corticosteroid	1.08	0.79-1.47	0.632						
Imidazole	1.00	0.77-1.29	0.985						
Estrogen	0.78	0.61-1.00	0.047						
Radiation therapy	1.00	0.87-1.16	0.952						
Visceral disease	1.31	1.09-1.56	0.003	1.33	1.11-1.58	0.002	1.33	1.11-1.58	0.001
Bone disease	1.05	0.82-1.35	0.691						
Lymph node/soft tissue disease	1.11	0.96-1.28	0.172	1.10	0.96-1.27	0.164	1.14	1.00-1.32	0.058

* Final model of choice

† Adjusted for random effect of individual trials

Table 5. Interaction between race and age on overall survival

	Mixed-effect Cox model with interaction term†						
	Black		White				
	Events	No. of patients	Events	No. of patients	HR	95% CI	p-value
18-64 years black vs white	14	33	280	515	0.82	0.48-1.41	0.477
65-74 years black vs white	21	37	343	752	1.10	0.71-1.72	0.670
≥ 75 years black vs white	6	19	190	395	0.51	0.23-1.15	0.104
PSA					1.05	1.00-1.11	0.039
ALP					1.42	1.30-1.54	<0.001
Hb					0.16	0.09-0.28	<0.001
Gonadotropin					0.78	0.66-0.92	0.004
Visceral disease					1.33	1.12-1.59	0.001
Lymph node/soft tissue disease					1.14	1.00-1.32	0.058

† Adjusted for random effect of individual trials

Table 6. Interaction between race and visceral disease on overall survival

	Mixed-effect Cox model with interaction term†						
	Black		White				
	Events	No. of patients	Events	No. of patients	HR	95% CI	p-value
Non-visceral disease	35	78	653	1351	0.84	0.60-1.19	0.323
Visceral disease	6	11	160	311	0.96	0.42-2.17	0.917
18-64 years					1	--	--
65-74 years					0.91	0.78-1.06	0.211
≥ 75 years					1.05	0.87-1.26	0.628
PSA					1.05	1.00-1.10	0.045
ALP					1.42	1.30-1.54	<0.001
Hb					0.16	0.09-0.28	<0.001
Gonadotropin					0.77	0.65-0.92	0.003
Lymph node/soft tissue disease					1.14	0.99-1.31	0.060

† Adjusted for random effect of individual trials

Table 7. Interaction between race and PSA response on overall survival

Mixed-effect Cox model with interaction term†

	Responders		Non-responders		HR	95% CI	p-value
	Events	No. of patients	Events	No. of patients			
Black PSA responder vs non-responder	20	46	20	41	0.78	0.42-1.45	0.423
White PSA responder vs non-responder	364	825	439	812	0.54	0.47-0.62	<0.001
18-64 years					1	--	--
65-74 years					0.92	0.79-1.08	0.309
≥ 75 years					1.04	0.87-1.25	0.686
PSA					1.03	0.98-1.08	0.272
ALP					1.46	1.34-1.58	<0.001
Hb					0.17	0.09-0.30	<0.001
Gonadotropin					0.76	0.64-0.91	0.003
Viseral disease					1.34	1.12-1.59	0.001
Lymph node/soft tissue disease					1.20	1.04-1.38	0.013

Table 8. Mixed-effect logistic regression models on the tendency of PSA response

	Full model, imputed data†			Selected model, imputed data†			Selected model, non-imputed data*†		
No. of patients	1774			1784			1716		
No. black/white	90/1684			92/1692			87/1629		
Variables	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Race (black vs white)	1.29	1.16-1.44	<0.001	1.29	1.17-1.43	<0.001	1.30	1.17-1.46	<0.001
Age group									
18-64	1	--	--	1	--	--	1	--	--
65-74	1.09	0.96-1.23	0.191	1.08	0.96-1.22	0.215	1.09	0.95-1.25	0.218
≥ 75	0.93	0.73-1.18	0.538	0.93	0.74-1.19	0.583	0.93	0.75-1.15	0.517
PSA	0.97	0.91-1.04	0.441	0.97	0.91-1.03	0.333	0.96	0.90-1.03	0.238
ALP	1.09	0.92-1.29	0.309	1.09	0.95-1.25	0.237	1.06	0.94-1.19	0.358
LDH	0.83	0.70-0.98	0.028	0.84	0.74-0.97	0.015			
Albumin	1.28	0.39-4.09	0.676						
Hb	2.87	1.47-5.59	0.002	3.76	1.72-8.19	0.001	4.34	2.26-8.35	<0.001
N/L ratio	0.98	0.79-1.22	0.863						
Creatinine	1.05	0.82-1.33	0.710	1.06	0.81-1.38	0.677	1.05	0.81-1.37	0.699
Total-bilirubin	1.28	1.05-1.55	0.013	1.26	1.06-1.49	0.009	1.22	1.04-1.44	0.016
Anti-androgen	1.19	0.93-1.41	0.213						
Glucocorticoid	1.08	0.84-1.39	0.544						
Gonadotropin	1.20	0.93-1.54	0.164						
Bisphosphonate	0.93	0.82-1.04	0.210						
Corticosteroid	0.86	0.17-4.48	0.862						
Imidazole	0.76	0.65-0.8	<0.001						
Estrogen	0.98	0.76-1.26	0.845						
Radiation therapy	1.24	1.01-1.53	0.041	1.24	1.01-1.53	0.037	1.29	1.01-1.64	0.039
Visceral disease	1.15	0.88-1.50	0.293	1.15	0.89-1.48	0.293	1.13	0.82-1.55	0.451
Bone disease	0.99	0.77-1.27	0.920						
Lymph node/soft tissue disease	1.04	0.79-1.38	0.766						

* Final model of choice

† Adjusted for random effect of individual trials

Table 9. Interaction between race and age on the tendency of PSA response

Mixed-effect logistic regression model with interaction term†

	Black		White				
	Events	No. of patients	Events	No. of patients	OR	95% CI	p-value
18-64 years black vs white	18	31	253	508	1.70	0.98-2.96	0.060
65-74 years black vs white	19	38	384	731	1.05	0.59-1.86	0.870
≥ 75 years black vs white	9	18	184	390	1.31	0.81-2.14	0.275
PSA					0.96	0.90-1.03	0.246
ALP					1.06	0.94-1.19	0.355
Hb					4.39	2.32-8.31	<0.001
Total-bilirubin					1.22	1.04-1.44	0.014
Creatinine					1.06	0.81-1.38	0.695
Radiation therapy					1.29	1.01-1.63	0.038
Visceral disease					1.29	0.82-1.54	0.456

† Adjusted for random effect of individual trials

Table 10. Interaction between race and visceral disease on the tendency of PSA response

Mixed-effect logistic regression model with interaction term†

	Black		White				
	Events	No. of patients	Events	No. of patients	OR	95% CI	p-value
Non-visceral disease	40	77	660	1323	1.27	1.13-1.43	<0.01
Visceral disease	6	10	161	306	1.61	0.88-2.96	0.124
18-64 years							
65-74 years							
≥ 75 years							
PSA					0.97	0.90-1.03	0.237
ALP					1.06	0.94-1.19	0.354
Hb					4.33	2.25-8.36	<0.001
Total-bilirubin					1.22	1.04-1.44	0.015
Creatinine					1.05	0.81-1.37	0.699
Radiation therapy					1.29	1.01-1.63	0.038

† Adjusted for random effect of individual trials

Figure 1. Kaplan-Meier survival analysis by race

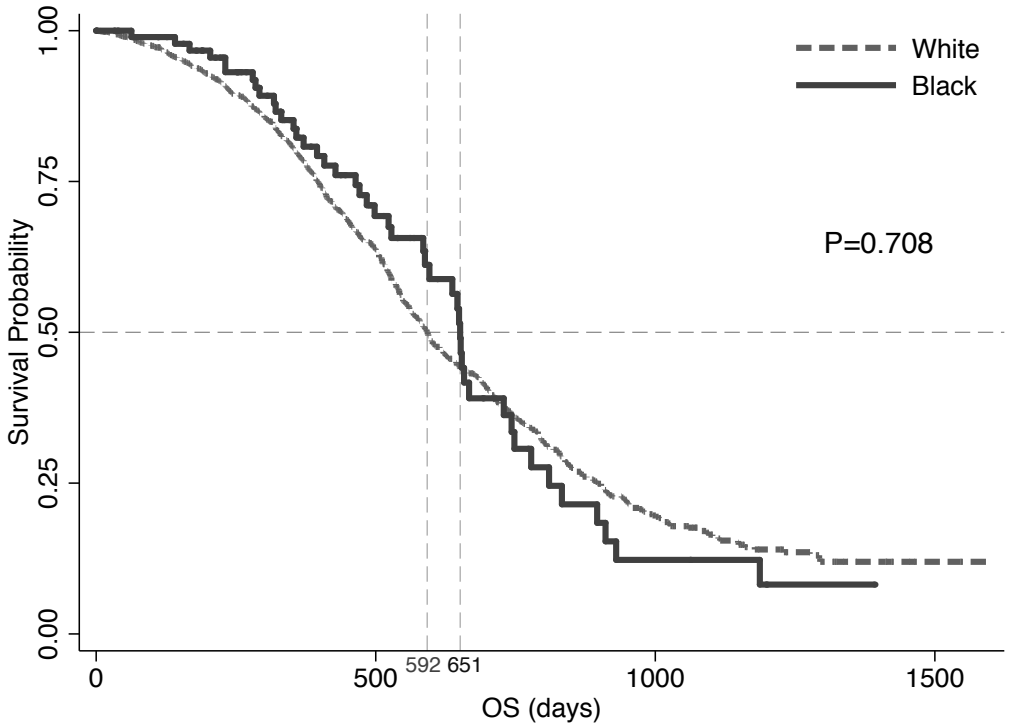


Figure 2. Hazard ratio for death, comparing black to white race, using a random effect model

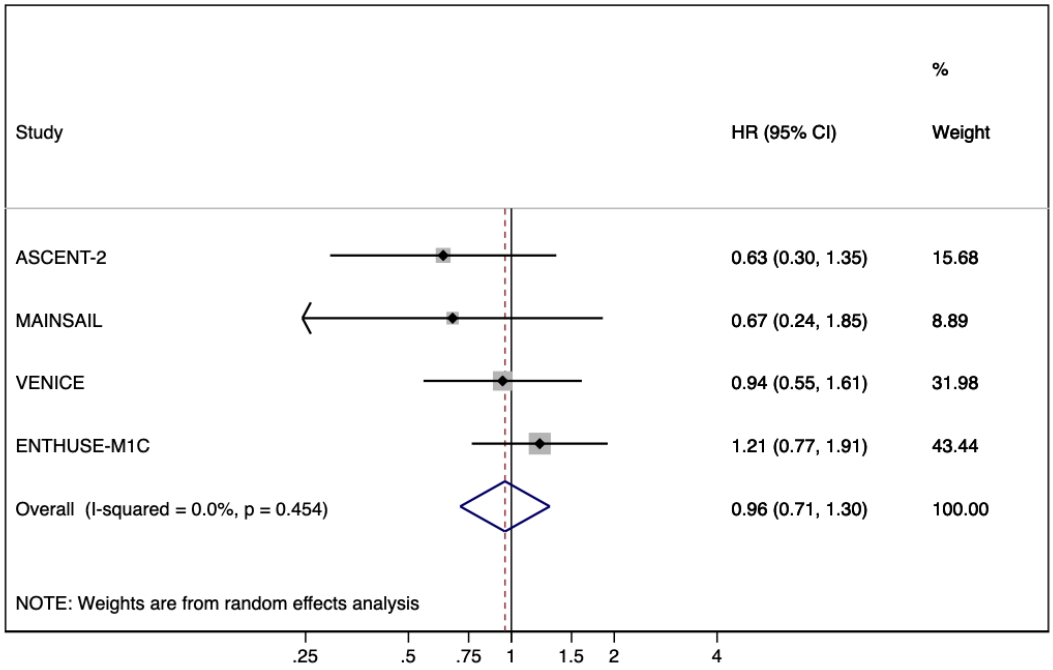


Figure 3. Kaplan-Meier survival analysis by race and PSA response

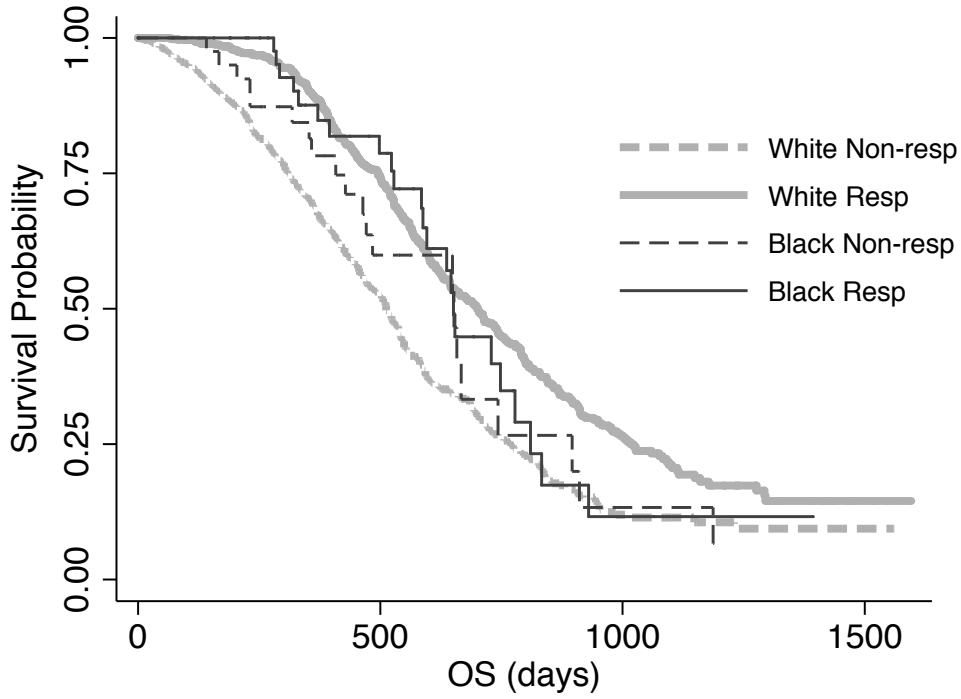


Figure 4. Odds ratio for PSA response, comparing black to white race, using a random effect model

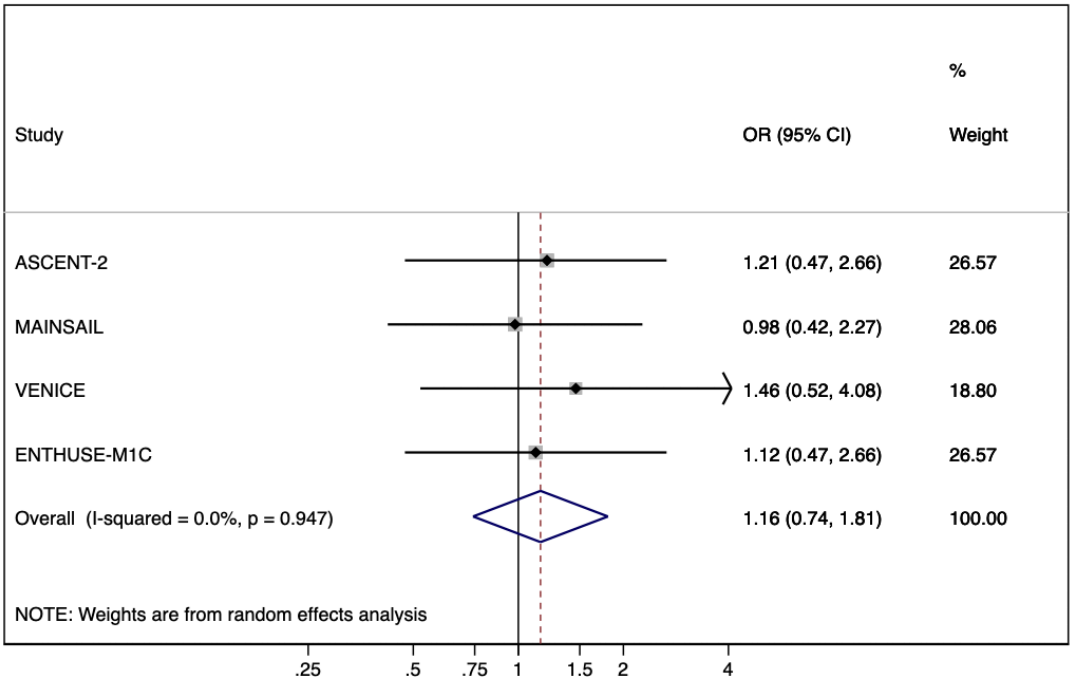


Figure 5. HR for death, comparing black to white men by age group and visceral disease in the interaction models

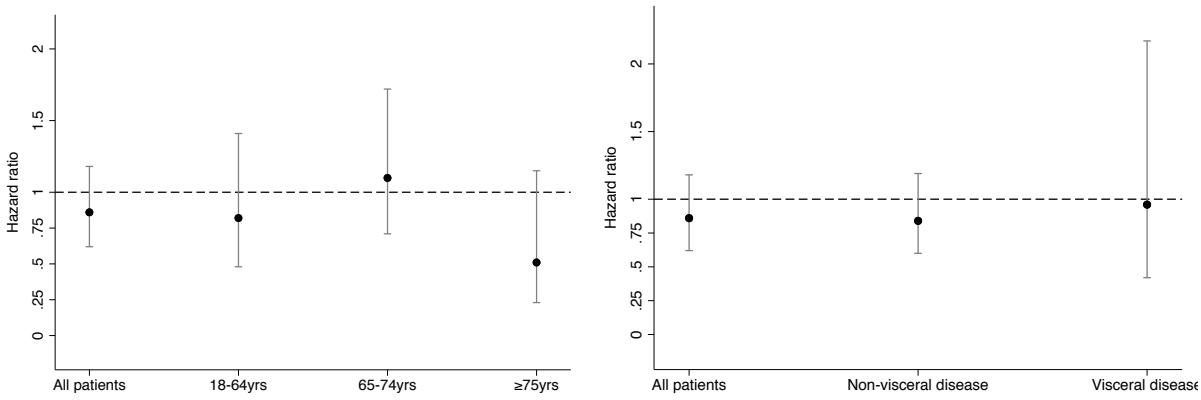


Figure 6. Prognostic value of PSA response by race in the interaction model

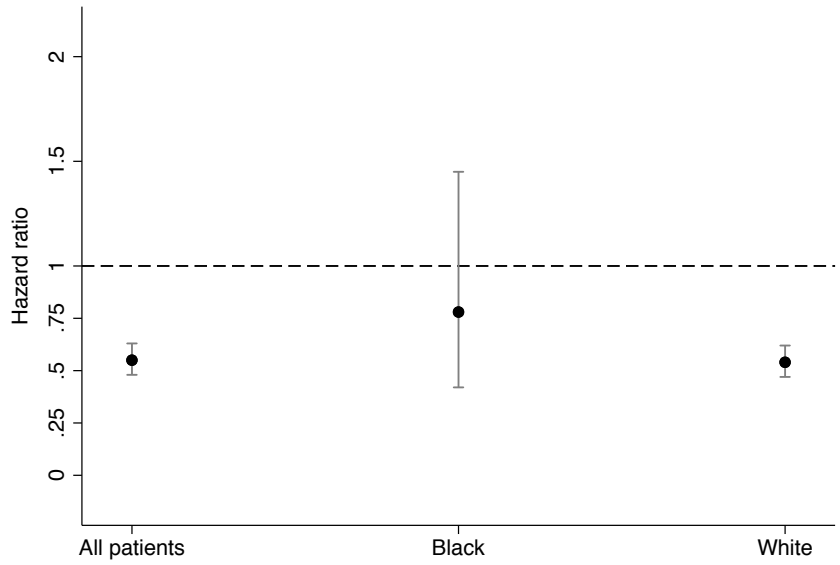
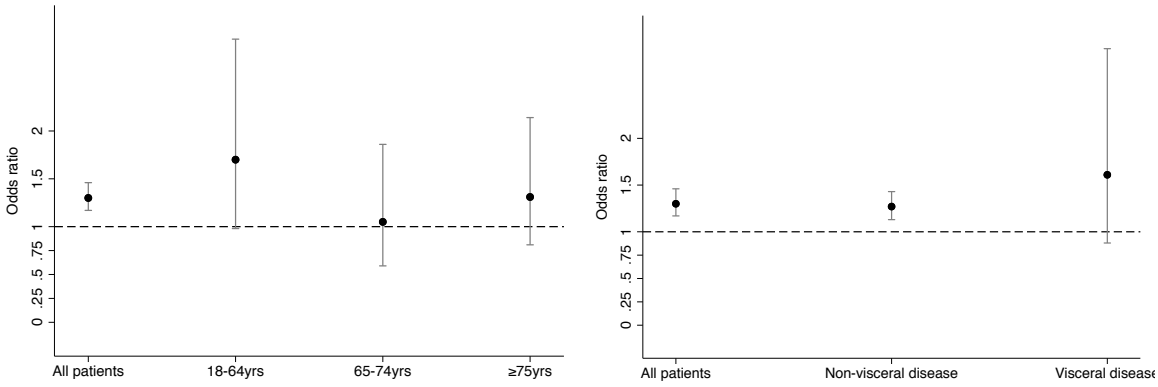


Figure 7. OR for PSA response, comparing black to white men by age group and visceral disease in the interaction models



6 References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017;67(1):7-30. doi:10.3322/caac.21387.

2. DeSantis CE, Siegel RL, Sauer AG, et al. Cancer statistics for African Americans, 2016: Progress and opportunities in reducing racial disparities. *CA Cancer J Clin*. 2016;66(4):290-308. doi:10.3322/caac.21340.

3. Karami S, Young HA, Henson DE. Earlier age at diagnosis: Another dimension in cancer disparity? *Cancer Detection and Prevention*. 2007;31(1):29-34. doi:10.1016/j.cdp.2006.11.004.

4. Robbins HA, Engels EA, Pfeiffer RM, Shiels MS. Age at Cancer Diagnosis for Blacks Compared With Whites in the United States. *J Natl Cancer Inst*. 2015;107(3):dju489. doi:10.1093/jnci/dju489.

5. Powell IJ, Bock CH, Ruterbusch JJ, Sakr W. Evidence supports a faster growth rate and/or earlier transformation to clinically significant prostate cancer in black than in white American men, and influences racial progression and mortality disparity. *J Urol*. 2010;183(5):1792-1796. doi:10.1016/j.juro.2010.01.015.

6. Sundi D, Ross AE, Humphreys EB, et al. African American men with very low-risk prostate cancer exhibit adverse oncologic outcomes after radical prostatectomy: should active surveillance still be an option for them? *J Clin Oncol*. 2013;31(24):2991-2997. doi:10.1200/JCO.2012.47.0302.

7. Vora A, Large T, Aronica J, et al. Predictors of Gleason score upgrading in a large African-American population. *Int Urol Nephrol*. 2013;45(5):1257-1262. doi:10.1007/s11255-013-0495-y.

8. Faisal FA, Sundi D, Cooper JL, et al. Racial disparities in oncologic outcomes after radical prostatectomy: long-term follow-up. *Urology*. 2014;84(6):1434-1441. doi:10.1016/j.urology.2014.08.039.

9. Wallace TA, Prueitt RL, Yi M, et al. Tumor immunobiological differences in prostate cancer between African-American and European-American men. *Cancer Res*. 2008;68(3):927-936. doi:10.1158/0008-5472.CAN-07-2608.

10. Powell IJ, Dyson G, Land S, et al. Genes Associated with Prostate Cancer Are Differentially Expressed in African American and European American Men. *Cancer Epidemiol Biomarkers Prev*. 2013;22(5):891-897. doi:10.1158/1055-9965.EPI-12-1238.

11. Sundi D, Kryvenko ON, Carter HB, Ross AE, Epstein JI, Schaeffer EM. Pathological examination of radical prostatectomy specimens in men with very low risk disease at biopsy reveals distinct zonal distribution of cancer in black American men. *J Urol*. 2014;191(1):60-67. doi:10.1016/j.juro.2013.06.021.

12. Freedland SJ, Isaacs WB. Explaining racial differences in prostate cancer in the United States: sociology or biology? *Prostate*. 2005;62(3):243-252. doi:10.1002/pros.20052.

13. Taksler GB, Keating NL, Cutler DM. Explaining racial differences in prostate cancer mortality. *Cancer*. 2012;118(17):4280-4289. doi:10.1002/cncr.27379.

14. Polednak AP. Black-white differences in survival from late-stage prostate cancer. *Ethn Dis*. 2003;13(2):220-225.

15. Wu T-H, Yang JC-H. Real-World or Controlled Clinical Trial Data in Real-World Practice. *J Thorac Oncol*. 2018;13(4):470-472. doi:10.1016/j.jtho.2018.02.009.

16. Wissing MD, Kluetz PG, Ning Y-M, et al. Under-representation of racial minorities in prostate cancer studies submitted to the US Food and Drug Administration to support potential marketing approval, 1993-2013. *Cancer*. 2014;120(19):3025-3032. doi:10.1002/cncr.28809.

17. Li J, Siegel DA, King JB. Stage-specific incidence rates and trends of prostate cancer by age, race, and ethnicity, United States, 2004-2014. *Ann Epidemiol*. 2018;28(5):328-330. doi:10.1016/j.annepidem.2018.03.001.

18. Wood CG, Wei SJ, Hampshire MK, Devine PA, Metz JM. The influence of race on the attitudes of radiation oncology patients towards clinical trial enrollment. *Am J Clin Oncol*. 2006;29(6):593-599. doi:10.1097/01.coc.0000236213.61427.84.

19. Rivers D, August EM, Sehovic I, Lee Green B, Quinn GP. A systematic review of the factors influencing African Americans' participation in cancer clinical trials. *Contemp Clin Trials*. 2013;35(2):13-32. doi:10.1016/j.cct.2013.03.007.

20. Thompson I, Tangen C, Tolcher A, Crawford E, Eisenberger M, Moinpour C. Association of African-American ethnic background with survival in men with metastatic prostate cancer. *J Natl Cancer Inst*. 2001;93(3):219-225.

21. Tangen CM, Hussain MHA, Higano CS, et al. Improved overall survival trends of men with newly diagnosed M1 prostate cancer: a SWOG phase III trial experience (S8494, S8894 and S9346). *J Urol*. 2012;188(4):1164-1169. doi:10.1016/j.juro.2012.06.046.

22. Halabi S, Small EJ, Vogelzang NJ, Barrier RC, George SL, Gilligan TD. Impact of race on survival in men with metastatic hormone-refractory prostate cancer. *Urology*. 2004;64(2):212-217. doi:10.1016/j.urology.2004.04.014.

23. Halabi S, Vogelzang NJ, Ou S-S, Kelly WK, Small EJ. Clinical outcomes by age in men with hormone refractory prostate cancer: a pooled analysis of 8 Cancer and Leukemia Group B (CALGB) studies. *J Urol*. 2006;176(1):81-86. doi:10.1016/S0022-5347(06)00566-0.

24. Halabi S, Dutta S, Tangen CM, et al. Overall Survival of Black and White Men With Metastatic Castration-Resistant Prostate Cancer Treated With Docetaxel. *J Clin Oncol*. 2019;37(5):403-410. doi:10.1200/JCO.18.01279.

25. Petrylak DP, Ankerst DP, Jiang CS, et al. Evaluation of prostate-specific antigen declines for surrogacy in patients treated on SWOG 99-16. *J Natl Cancer Inst*. 2006;98(8):516-521. doi:10.1093/jnci/djj129.

26. Armstrong AJ, Garrett-Mayer E, Ou Yang Y-C, et al. Prostate-specific antigen and pain surrogacy analysis in metastatic hormone-refractory prostate cancer. *J Clin Oncol*. 2007;25(25):3965-3970. doi:10.1200/JCO.2007.11.4769.

27. Collette L, Burzykowski T, Carroll KJ, et al. Is prostate-specific antigen a valid surrogate end point for survival in hormonally treated patients with metastatic prostate cancer? Joint research of the European Organisation for Research and Treatment of

Cancer, the Limburgs Universitair Centrum, and AstraZeneca Pharmaceuticals. *Journal of Clinical Oncology*. 2005;23(25):6139-6148. doi:10.1200/JCO.2005.08.156.

28. Francini E, Petrioli R, Rossi G, Laera L, Roviello G. PSA response rate as a surrogate marker for median overall survival in docetaxel-based first-line treatments for patients with metastatic castration-resistant prostate cancer: an analysis of 22 trials. *Tumour Biol*. 2014;35(11):10601-10607. doi:10.1007/s13277-014-2559-8.

29. Colloca G. Prostate-specific antigen kinetics as a surrogate endpoint in clinical trials of metastatic castration-resistant prostate cancer: a review. *Cancer Treatment Reviews*. 2012;38(8):1020-1026. doi:10.1016/j.ctrv.2012.03.008.

30. Scher HI, Morris MJ, Stadler WM, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. *Journal of Clinical Oncology*. 2016;34(12):JCO642702–1418. doi:10.1200/JCO.2015.64.2702.

31. Project Data Sphere https://projectdatasphere.org/projectdatasphere/html/about.

32. Schafer JL. *Analysis of Incomplete Multivariate Data*. Vol 72. CRC Press; 1997.

33. Vijayakumar S, Karrison T, Weichselbaum RR, Chan S, Quadri SF, Awan AM. Racial differences in prostate-specific antigen levels in patients with local-regional prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 1992;1(7):541-545.

34. Moul JW, Connelly RR, Mooneyhan RM, et al. Racial differences in tumor volume and prostate specific antigen among radical prostatectomy patients. *J Urol*. 1999;162(2):394-397.

35. Morgan TO, Jacobsen SJ, McCarthy WF, Jacobson DJ, McLeod DG, Moul JW. Age-specific reference ranges for serum prostate-specific antigen in black men. *New England Journal of Medicine*. 1996;335(5):304-310. doi:10.1056/NEJM199608013350502.

36. Beutler E, West C. Hematologic differences between African-Americans and whites: the roles of iron deficiency and alpha-thalassemia on hemoglobin levels and mean corpuscular volume. *Blood*. 2005;106(2):740-745. doi:10.1182/blood-2005-02-0713.

37. Reading SR, Porter KR, Hsu J-WY, Wallner LP, Loo RK, Jacobsen SJ. Racial and Ethnic Variation in Time to Prostate Biopsy After an Elevated Screening Level of Serum Prostate-specific Antigen. *Urology*. 2016;96:121-127. doi:10.1016/j.urology.2016.06.008.

38. Jindal T, Kachroo N, Sammon J, et al. Racial differences in prostate-specific antigen-based prostate cancer screening: State-by-state and region-by-region analyses. *Urol Oncol*. 2017;35(7):460.e9-460.e20. doi:10.1016/j.urolonc.2017.01.023.

39. Fowler JE, Bigler SA, Renfroe DL, Dabagia MD. Prostate specific antigen in black and white men after hormonal therapies for prostate cancer. *J Urol*. 1997;158(1):150-154. doi:10.1097/00005392-199707000-00047.

40. Cross CK, Shultz D, Malkowicz SB, et al. Impact of race on prostate-specific antigen outcome after radical prostatectomy for clinically localized adenocarcinoma of the prostate. *Journal of Clinical Oncology*. 2002;20(12):2863-2868. doi:10.1200/JCO.2002.11.054.

41. Hussain M, Smith DC, El-Rayes BF, et al. Neoadjuvant docetaxel and estramustine chemotherapy in high-risk/locallyadvanced prostate cancer. *Urology*. 2003;61(4):774-780.

42. McGuire SE, Lee AK, Cerne JZ, et al. PSA response to neoadjuvant androgen deprivation therapy is a strong independent predictor of survival in high-risk prostate cancer in the dose-escalated radiation therapy era. *Int J Radiat Oncol Biol Phys*. 2013;85(1):e39-e46. doi:10.1016/j.ijrobp.2012.08.036.

43. Ramalingam S, Humeniuk MS, Hu R, et al. Prostate-specific antigen response in black and white patients treated with abiraterone acetate for metastatic castrate-resistant prostate cancer. *Urol Oncol*. 2017;35(6):418-424. doi:10.1016/j.urolonc.2016.12.016.

Biography

Ting-Hui Wu was born in 1984 in Taiwan.

Ting-Hui received a M.D. degree from the National Taiwan University and completed his residency in internal medicine and fellowship in medical oncology at the National Taiwan University Hospital. He had also received specialized training in clinical trials, including the Paul Carbon Academy, Australia & Asia Pacific Clinical Oncology Research Development Workshop, and the clinical trial certificate at the Johns Hopkins Bloomberg School of Public Health. His prior works focused on utilizing clinical trial data and real-world evidence to generate medical knowledge that potentially change the way of clinical practice.

In 2017, Ting-Hui started his Master of Science program in epidemiology at the Johns Hopkins Bloomberg School of Public Health.